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THE BIOLOGY OF DEATH—VI. EXPERIMENTAL STUDIES ON THE DURATION OF LIFE[1]

By Professor RAYMOND PEARL
THE JOHNS HOPKINS UNIVERSITY

1. Inheritance of Duration of Life in Drosophila

IN the last paper there was presented indubitable proof that inheritance is a major factor in determining the duration of life in man. The evidence, while entirely convincing and indeed in the writer's opinion critically conclusive, must be, in the nature of the case, statistical in its nature. Experimental inquiries into the duration of human life are obviously impossible. Public opinion frowns upon them in the first place, and even if this difficulty were removed man would furnish poor material for the experimental study of this particular problem because he lives too long. It is always important, however, as a general principle, and particularly so in the present instance, to check one's statistical conclusions by independent experimental evidence. This can be successfully done, when one's problem is longevity, only by choosing an animal whose life-span relative to that of man is a short one, and in general the briefer it is the better suited will the animal be for the purpose.

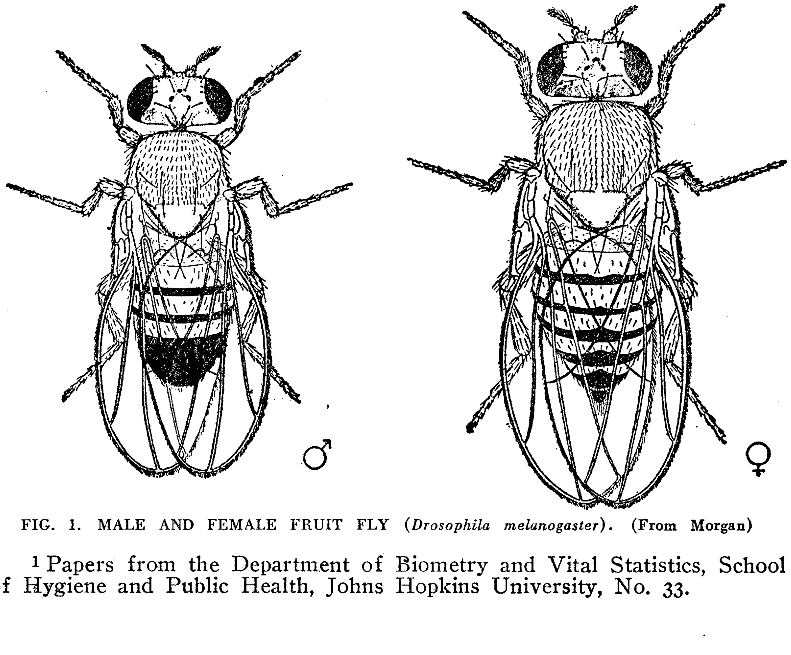

FIG. 1. MALE AND FEMALE FRUIT FLY (*Drosophila melanogaster*). (From Morgan)

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[1] Papers from the Department of Biometry and Vital Statistics, School of Hygiene and Public Health, Johns Hopkins University, No. 33.

An organism which rather completely fulfils the requirements of the case, not only in respect of the shortness of the life span, but also in other ways, such as ease of handling, feeding, housing, etc., is the common "fruit" or "vinegar" fly, *Drosophila melanogaster*. This creature, which every one has seen hovering about bananas and other fruit in fruit shops, has lately attained great fame and respectability as a laboratory animal, as a result of the brilliant and extended investigations of Morgan and his students upon it, in an analysis of the mechanism of heredity. *Drosophila* is a small fly, perhaps one fourth as large as the common house fly. It has striking red eyes, a brownish body, and wings of length and form varying in different strains. It lives normally on the surface of decaying fruit of all sorts, but because of a more or less well marked preference for banana it is sometimes called the "banana" fly. While it lives on decaying fruit surfaces its food is mainly not the fruit itself, but the yeast which is always growing in such places.

The life cycle of the fly is as follows: The egg laid by the female on some fairly dry spot on the food develops in about 1 day into a larva. This larva or maggot squirms about and feeds in the rich medium in which it finds itself for about 3 to 4 days and then forms a pupa. From the pupa the winged imago or adult form emerges in about 4 or 5 days. The female generally begins to lay eggs within the first 24 hours after she is hatched. So then we have about 8 to 10 days as the minimum time duration of a generation. The whole cycle from egg to egg, at ordinary room temperature, falls within this 10-day period with striking accuracy and precision.

The duration of life of the adult varies in an orderly manner from less than 1 day to over 90 days. The span of life of *Drosophila* quantitatively parallels in an extraordinary way that of man, with only the difference that life's duration is measured with different yardsticks in the two cases. Man's yardstick is one *year* long, while *Drosophila's* is one *day* long. A fly 90 days old is just as decrepit and senile, for a fly, as a man 90 years old is in human society.

This parallelism in the duration of life of *Drosophila* and man is well shown in Fig. 2, which represents a life table for adult flies of both sexes. The survivorship, or l_x figures, are the ones plotted. The curves deal only with flies in the adult or imago stage, after the completion of the larval and pupal periods. The curve is based upon 3,216 female and 2,620 male flies, large enough numbers to give reliable and smooth results. We note at once that in general the curve has the same form as the corresponding l_x curve from human mortality tables. The most striking difference is in the absence from the fly curves of the heavy infant mortality which characterizes the human curve. There is no specially sharp drop in the curve at the beginning of the life cycle,

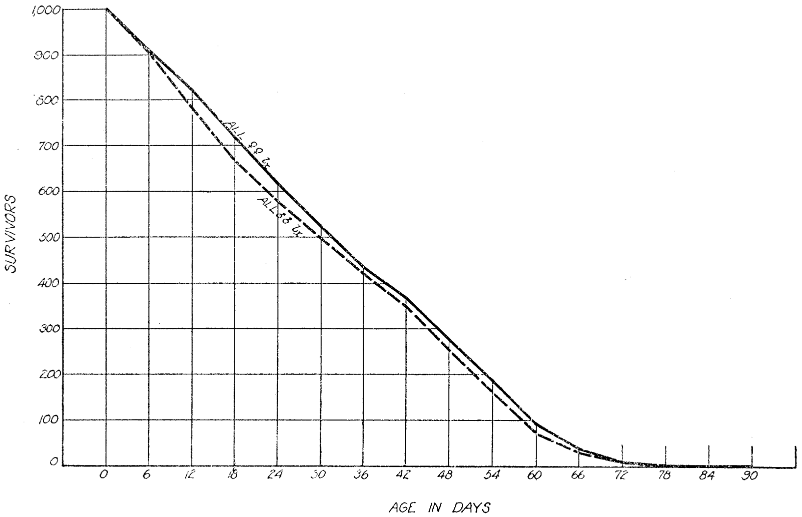

FIG. 2. LIFE LINES FOR *Drosophila melanogaster*, SHOWING THE SURVIVORS AT DIFFERENT AGES OUT OF 1000 BORN AT THE SAME TIME

such as has been seen in the l_x curve for man in an earlier paper in this series. This might at first be thought to be accounted for by the fact that the curve begins after the infantile life of the fly, but it must be remembered that the human l_x line begins at birth, and no account is taken of the mortality *in utero*. Really the larval and pupal stages of the fly correspond rather to the foetal life of a human being than to the infant life, so that one may fairly take the curves as covering comparable portions of the life span in the two cases and reach the conclusion that there is not in the fly an especially heavy incidence of mortality in the infant period of life, as there is in man. The explanation of this fact is, without doubt, that the fly when it emerges from the pupal stage is completely able to take care of itself. The baby is, on the contrary, in an almost totally helpless condition at the same relative age.

It is further evident that at practically all ages in *Drosophila* the number of survivors at any given age is higher among the females than among the males. This, it will be recalled, is exactly the state of the case in human mortality. The speed of the descent of the *Drosophila* curve slows off in old age, just as happens in the human life curve. The rate of descent of the curve in early middle life is somewhat more rapid with the flies than in the case of human beings, but as will presently appear there are some strains of flies which give curves almost identical in this respect with the human mortality curves. In the life curves of Figure 2, all different degrees of inherited or constitutional variation in longevity are included together. More accurate pictures of the true state of affairs will appear when we come, as we presently shall, to deal with groups of individuals more homogeneous in respect of their hereditary constitutions.

Having now demonstrated that the incidence of mortality is in general similar in the fly *Drosophila* to what it is in man, with a suitable change of unit of measure, we may proceed to examine some of the evidence regarding the inheritance of duration of life in this organism. The first step in such an examination is to determine what degree of natural variation of an hereditary sort exists in a general fly population in respect of this characteristic. In order to do this it is necessary to isolate individual pairs, male and female, breed them together and see whether, between the groups of offspring so obtained, there are genetic differences in respect of duration of life which persist through an indefinite number of generations. This approaches closely to the process called by geneticists the testing of pure lines. In such a process the purpose is to reduce to a minimum the *genetic* diversity which can possibly be exhibited in the material. In a case like the present, the whole amount of genetic variation in respect of duration of life which can appear in the offspring of a single pair of parents is only that which can arise by virtue of its prior existence in the parents themselves individually, and from the combination of the germinal variation existing in the two parents one with another. We may call the offspring, through successive generations, of a single pair of parents a line of descent. If, when kept under identical environmental conditions such lines exhibit widely different average durations of life, and if these differences reappear with constancy in successive generations, it may be justly concluded that the basis of these differences is hereditary in nature, since by hypothesis the environment of all the lines is kept the same. In consequence of the environmental equality whatever differences do appear must be inherently genetic.

The manner in which these experiments are performed may be of interest. An experiment starts by placing two flies, brother and sister, selected from a stock bottle, together in a half-pint milk bottle. At the bottom of the bottle is a solidified, jelly-like mixture of agar-agar and boiled and pulped banana. On this is sown as food some dry yeast. A bit of folded filter paper in the bottle furnishes the larvae opportunity to pupate on a dry surface. About ten days after the pair of flies have been placed in this bottle fully developed offspring in the imago stage begin to emerge. The day before these offspring flies are due to appear, the original parent pair of flies are removed to another bottle precisely like the first, and the female is allowed to lay another batch of eggs over a period of about nine days. In the original bottle there will be offspring flies emerging each day, having developed from the eggs laid by the mother on each of the successive days during which she was in the bottle. Each morning the offspring flies which have emerged during the preceding twenty-four hours are transferred to a small bottle. This has, just as the larger one, food material at the bottom and like the larger one is closed with a cotton stopper. All of the offspring flies in one of these small bottles are obviously of the same age, because they were born at the same time, using this term "born" to denote emergence from the pupal stage as imagines. Each following day these small bottles are inspected. Whenever a dead fly is found it is removed and a record made in proper form of the fact that its death occurred, and its age and sex are noted. Finally, when all the flies in a given small bottle have died that bottle is discarded, as the record of the duration of life of each individual is then complete. All the bottles are kept in electric incubators at a constant temperature of 25° C., the small bottles being packed for convenience in wire baskets. All have the same food material, both in quality and quantity, so that the environmental conditions surrounding these flies during their life may be regarded as substantially constant and uniform for all.

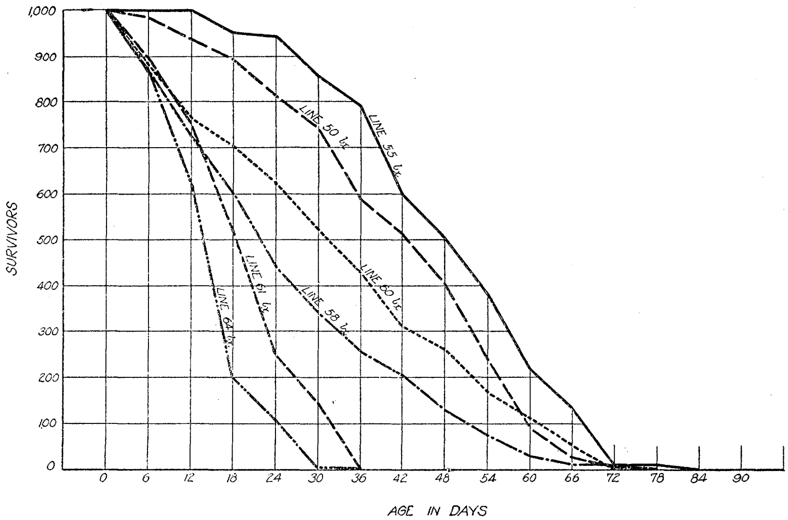

FIG. 3. LIFE LINES FOR DIFFERENT INBRED LINES OF DESCENT IN *Drosophila*

Fgure 3 shows the survival frequency, or l_x line of a life table, for six different lines of *Drosophila,* which have been bred in my laboratory. Each line represents the survival distribution of the offspring of a single brother and sister pair mated together. In forming a line a brother and sister are taken as the initial start because by so doing the amount of genetic variation present in the line at the beginning is reduced to the lowest possible minimum. It should be said that in all of the curves in Figure 3 both male and female offspring are lumped together. This is justifiable for illustrative purposes because of the small difference in the expectation of life at any age between the sexes. The line of descent No. 55 figured at the top of the diagram gives an l_x line extraordinarily like that for man, with the exception of the omission of the sharp drop due to infantile mortality at the beginning of the curve. The extreme duration of life in this line was 81 days, reached by a female fly. The l_x line drops off very slowly until age 36 days. From that time on the descent is more rapid until 72 days of age are reached when it slows up again. Lines 50, 60, and 58 show l_x curves all descending more rapidly in the early part of the life cycle than that for line 55, although the maximum degree of longevity attained is about the same in all of the four first curves. The general shape of the l_x curves changes however, as is clearly seen if we contrast line 55 with line 58. The former is concave to the base through nearly the whole of its course, whereas the l_x curve for line 58 is convex to the base practically throughout its course. While, as is clear from the diagram, the maximum longevity attained is about the same for all of these upper four lines, it is equally obvious that the mean duration of life exhibited by the lines falls off as we go down the diagram. The same process, which is in operation between lines 55 and 58, is continued in an even more marked degree in lines 61 and 64. Here not only is the descent more rapid in the early part of the l_x curve, but the maximum degree of longevity attained is much smaller, amounting to about half of that attained in the other four lines. Both lines 61 and 64 tend to show in general a curve convex to the base, especially in the latter half of their course.

Since each of these lines of descent continues to show through successive generations, for an indefinite time, the same types of mortality curves and approximately the same average durations of life, it may safely be concluded that there are well marked hereditary differences in different strains of the same species of *Drosophila* in respect of duration of life. Passing from the top to the bottom of the diagram the average expectation of life is reduced by about two-thirds in these representative curves. For purposes of experimentation, each one of these lines of descent becomes comparable to a chemical reagent. They have a definitely fixed standard duration of life, each peculiar to its own line and determined by the hereditary constitution of the individual in respect of this character. We may, with entire justification, speak of the flies of line 64 as hereditarily and permanently short-lived, and those of line 55 as hereditarily long-lived.

Having established so much, the next step in the analysis of the mode of inheritance of this character is obviously to perform a Mendelian experiment by crossing an hereditarily short-lived line with a hereditarily long-lived line, and follow through in the progeny of successive generations the duration of life. If the character follows the ordinary course of Mendelian inheritance, we should expect to get in the second offspring generation a segregation of different types of flies in respect of their duration of life.

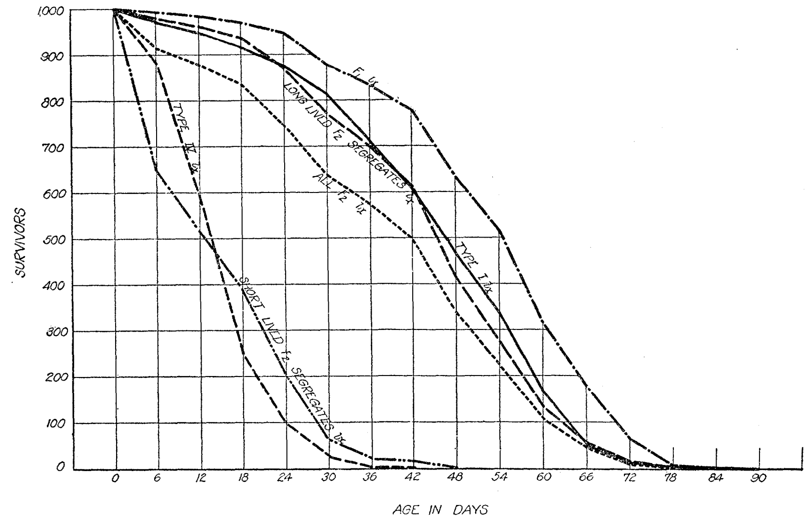

FIG. 4. LIFE LINES SHOWING THE RESULT OF MENDELIAN EXPERIMENTS ON THE DURATION OF LIFE IN *Drosophila*. Explanation in text

Figure 4 shows the result of such Mendelian experiment performed on a large scale. In the second line from the top of the diagram, labelled "Type I l_x," we see the mortality curve for an hereditarily long-lived pure strain of individuals. At the bottom of the diagram the "Type IV l_x" line gives the mortality curve for one of our hereditarily short-lived strains. Individuals of Type I and Type IV were mated together. The result in the first offspring hybrid generation is shown by the line at the top of the diagram marked "F_1 l_x." The F_1 denotes that this is the mortality curve of the *first filial generation* from the cross. It is at once obvious that these first generation hybrids have a greater expectation of life at practically all ages than do either of the parent strains mated together to produce the hybrids. This result is exactly comparable to that which has for some time been known to occur in plants, from the researches particularly of Professor E. M. East of Harvard University with maize. East and his students have worked out very thoroughly the cause of this increased vigor of the first hybrid generation and show that it is directly due to the mingling of different germ plasms.

The average duration of life of the Type I original parent stock is 44.2 ± .4 days. The average duration of life of the short-lived Type IV flies is 14.1 ± .2 days, or only about one third as great as that of the other stock. The average duration of life of the first hybrid generation shown in the F_1 l_x line is 51.5 ± .5 days. So that there is an increase in average duration of life in the first hybrid generation, over that of the long-lived parent, of approximately 7 days. In estimating the significance of this, one should remember that a day in the life of a fly corresponds, as has already been pointed out, almost exactly to a year in the life of a man.

When individuals of the first hybrid generation are mated together to get the second, or F_2 hybrid generation we get a group of flies which, *if taken all together*, give the mortality curve shown in the line at about the middle of the diagram, labelled "All F_2 l_x." It, however, tells us little about the mode of inheritance of the character if we consider all the individuals of the second hybrid generation together, because really there are several kinds of flies present in this second hybrid generation. There are sharply separated groups of long-lived flies and of short-lived flies. These have been lumped together to give the "All F_2 l_x" line. If we consider separately the long-lived second generation group and the short-lived second generation group we get the results shown in the two lines labelled "Long-lived F_2 Segregates l_x," and "Short-lived F_2 Segregates l_x." It will be noted that the long-lived F_2 segregates have a mortality curve which almost exactly coincides with that of the original parent Type I stock. In other words, in the second generation after the cross of the long-lived and short-lived types a group of animals appears having almost identically the same form of mortality curve as that of one of the original parents in the cross. The mean duration of life of this long-lived second generation group is 43.3 ± .4 days, while that of the original long-lived stock was 44.2 ± .4 days. The short-lived F_2 segregates shown at the bottom of the diagram give a mortality curve essentially like that of the original short-lived parent strain. The two curves wind in and about each other, the F_2 flies showing a more rapid descent in the first half of the curve and a slower descent in the latter half. In general, however, the two are very clearly of the same form. The average duration of life of these short-lived second generation segregates is 14.6 ± .6 days. This, it will be recalled, is almost identically the same average duration of life as the original parent Type IV gave, which was 14.1 ± .2 days.

It may occur to one to wonder how it is possible to pick out the long-lived and short-lived segregates in the second generation. This is done by virtue of the correlation of the duration of life of these flies with certain external bodily characters, particularly the form of the wings, so that this arrangement of the material can be made with perfect ease and certainty.

These results show in a clear manner that duration of life, in *Drosophila* at least, is inherited essentially in accordance with Mendelian laws, thus fitting in with a wide range of other physical characters of the animal which have been thoroughly studied, particularly by Morgan and his students. Such results as these just shown constitute the best kind of proof of the essential point which we are getting at—namely, the fact that duration of life is a normally inherited character.

I do not wish at this time to go into any discussion of the details of the Mendelian mechanism for this character, in the first place, because it is too complicated and technical a matter for discussion here,[2] and in the second place, because the investigations are far from being completed yet. I wish here and now merely to present the demonstration of the broad general fact that duration of life is inherited in a normal Mendelian manner in these fly populations. The first evidence that this was the case came from some work of Dr. R. R. Hyde with *Drosophila* some years ago. The numbers involved in his experiment, however, were much smaller than those of the present experiments, and the preliminary demonstration of the existence of pure strains relative to duration of life in *Drosophila* was not undertaken by him. Hyde's results and those here presented are entirely in accord.

With the evidence which has now been presented regarding the inheritance of life in man and in *Drosophila* we may let that phase of the subject rest. The evidence is conclusive of the broad fact, beyond any question I think, coming as it does from such widely different types of life, and arrived at by such totally different methods as the statistical, on the one hand, and the experimental, on the other. We may safely conclude that the primary agent concerned in the winding up of the vital clock, and by the winding determining primarily and fundamentally how long it shall run, is heredity. The best insurance of longevity is beyond question a careful selection of one's parents and grandparents.

2. Bacteria and Duration of Life in Drosophila

But clocks may be stopped in other ways than by running down. It will be worth while to consider with some care a considerable mass of most interesting, and in some respects even startling, experimental data, regarding various ways in which longevity may be influenced by external agents. Since we have just been considering *Drosophila* it may be well to consider the experimental evidence regarding that form first. It is an obviously well-known fact that bacteria are responsible in all higher organisms for much organ breakdown and consequent death. An infection of some particular organ or organ system occurs, and the disturbance of the balance of the whole so brought about finally results in death. But is it not possible that we overrate the importance of bacterial invasion in determining, in general and in the broadest sense, the average duration of life? May it not be that when an organ system breaks down under stress of bacterial toxins, that it is in part at least, perhaps primarily, because for internal organic reasons the resistance of that organ system to bacterial invasion has normally and naturally reached such a low point that its defenses are no longer adequate? All higher animals live constantly in an environment far from sterile. Our mouths and throats harbor pneumonia germs much of the time, but we do not all or always have pneumonia. Again it may fairly be estimated that of all persons who attain the age of 35, probably at least 95 per cent. have at some time or other been infected with the tubercle bacillus, yet only about one in ten breaks down with active tuberculosis.

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[2] Full technical details and all the numerical data regarding these and other *Drosophila* experiments referred to in this and other papers in the series, will shortly be published elsewhere.

What plainly is needed in order to arrive at a just estimate of the relative influence of bacteria and their toxins in determining the average duration of life is an experimental inquiry into the effect of a bacteria-free, sterile mode of life. Metchnikoff has sturdily advocated the view that death in general is a result of bacterial intoxication. Now a bacteria free existence is not possible for man. But it is possible for certain insects, as was first demonstrated by Bogdanow, and later confirmed by Delcourt and Guyenot. If one carefully washes either the egg or the pupa of *Drosophila* for 10 minutes in a strong antiseptic solution, say 85 per cent. alcohol, he will kill any germs which may be upon the surface. If the bacteria-free egg or pupa is then put into a sterile receptacle, containing only sterile food material and a pure culture of yeast, development will occur and presently an adult imago will emerge. Adult flies raised in this way are sterile. They have no bacteria inside or out. Normal healthy protoplasm is normally sterile, so what is inside the fly is bound to be sterile on that account, and by the use of the antiseptic solution what bacteria were on the outside have been killed.

The problem now is, how long on the average do such sterile specimens of *Drosophila* live in comparison with the ordinary fly, which is throughout its adult life as much beset by bacteria relatively as is man himself, it being premised that in both cases an abundance of proper food is furnished and that in general the environmental conditions other than bacterial are made the same for the two sets? Fortunately, there are some data to throw light upon this question from the experiments of Loeb and his associate Northrop on the duration of life in this form, taken in connection with experiments in the writer's laboratory.

Loeb and Northrop show that a sample of 70 flies, of the *Drosophila* with which they worked, which were proved by the most careful and critical of tests to have remained entirely free of bacterial contamination throughout their lives, exhibited, when grown at a constant temperature of 25° C. *an average duration of life of 28.5 days.* In our experiments 2620 male flies, of all strains of *Drosophila* in our cultures taken together, thus giving a fair random sample of genetically the whole *Drosophila* population, gave an average duration of life at the same constant temperature of 25° C. of 31.3 ± .3 days, and 3216 females under the same temperature lived an average of 33.0 ± .2 days. These were all non-sterile flies, subject to all the bacterial contamination incident to their normal laboratory environment, which we have seen to be a decaying germ-laden mass of banana pulp and agar. It is thought to be fairer to compare a sample of a general population with the Loeb and Northrop figures rather than a pure strain because probably their *Drosophila* material was far from homozygous in respect of the genes for duration of life.

The detailed comparisons are shown in Table 1.

TABLE 1

Average duration of life of Drosophila in the imago stage at 25° C.

Experimental group	Mean duration of life in days	Number of flies
Sterile (Loeb and Northrop)	28.5	70
Non-sterile, males, all genetic lines (Pearl)	31.3	2620
Non-sterile, females, " " " "	33.0	3216
Non-sterile, both sexes, " " " "	32.2	5836
Difference in favor of non-sterile	3.7	....
Probable error of difference about	± 1.0	....

We reach the conclusion that bacteria-free *Drosophila* live no longer on the average, and indeed perhaps even a little less long, under otherwise the same constant environmental conditions, than do normal non-sterile—indeed germ-laden—flies. This result is of great interest and significance. It emphasizes in a direct experimental manner that in a *broad biological sense* bacteria play but an essentially accidental role in determining length of the span of life in comparison with the influence of heredity. There is every reason to believe that if the same sort of experiment were possible with man as material, somewhat the same sort of result in broad terms would appear.

3. Poverty and Duration of Life

But we must take care lest we seem to convey the impression that no sort of environmental influence can affect the average duration of life. Such a conclusion would be manifestly absurd. Common sense tells us that environmental conditions in general can, and under some circumstances, do exert a marked influence upon expectation of life. A recent study of great interest and suggestiveness, if perhaps some lack of critical soundness, by the eminent Swiss statistician, Hersch, well illustrates this. Hersch became interested in the relation of poverty to mortality. He gathered data from the 20 arrondissements of the City of Paris in respect of the following points, among others:

a. Percentage of families not paying a personal property tax.
b. Death rate per 1000 from all causes.
c. Still births per 1000 living births.

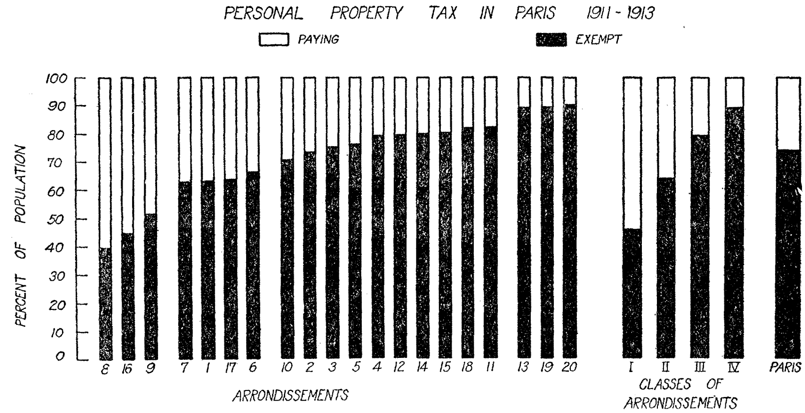

FIG. 5. DISTRIBUTION OF POVERTY IN PARIS (1911-13) AS INDICATED BY EXEMPTION FROM PERSONAL PROPERTY TAX. (After Hersch)

Figure 5 shows in the black the percentage of families too poor to have any personal property tax assessed, first for each arrondissement separately, then at the right in broader bars for the four groups of arrondissements separated by wider spaces in the detailed diagram, and finally for Paris as a whole. It will be seen that the poverty of the population, measured by the personal property yardstick, is least at the lefthand end of the diagram, where the smallest percentages of families are exempted from the tax, and greatest at the right hand end, where scarcely any of the population is well enough to do to pay this tax.

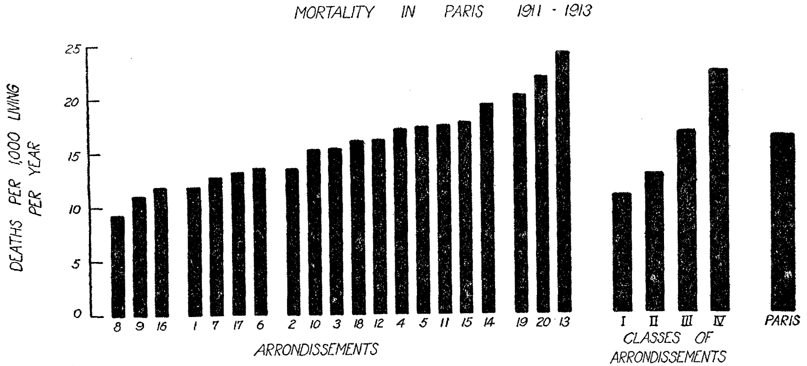

FIG. 6. DEATH RATES IN PARIS (1911-13) FROM ALL CAUSES. (After Hersch)

Figure 6 shows the death rates from all causes for the same arrondissements and the same groups. It is at once apparent that the black bars in this group run in a parallel manner to what they did in the preceding one. The poorest districts have the highest death rates, the richest districts the lowest death rates, and districts intermediate in respect of poverty are also intermediate in respect of mortality. On the face of the evidence there would seem to be here complete proof of the overwhelmingly important influence upon duration of life of degree of poverty, which is perhaps the most potent single environmental factor affecting civilized man to-day. But, alas, pitfalls proverbially lurk in statistics. Before we can accept this so alluring result and go along with our author to his final somewhat stupendous conclusion that if there were no poverty the death rate from certain important causes, as for example tuberculosis, would forthwith become *zero*, we must exercise a little inquisitive caution. What evidence is there that the inhabitants of the districts showing a high poverty rate are not *biologically* as well as economically differentiated from the inhabitants of districts with a low poverty rate? And again what is the evidence that it is not such biological differentiation rather than the economic which determines the death rate differences in the two cases? Unfortunately, our author gives us no whit of evidence on these obviously so important points. He merely assumes, because of the facts shown, that if some omnipotent spook were to transpose all the inhabitants of the Menilmontant arrondissement to the Elysee arrondissement, and *vice versa* for example, and were to permit each group to annex the worldly goods of the dispossessed group, then the death rates would be forthwith interchanged. There is no real evidence that any such result would follow at all. Probably from what we know from more critical studies than this of the relation of social and economic conditions to mortality, each group would exhibit under the new circumstances a death rate not far different from what it had under the old conditions. One can not shake in the slightest degree from its solidly grounded foundation the critically determined fact of the paramount importance of the hereditary factor in determining rates of mortality, which have been summarized in this and the preceding paper, by any such evidence as that of Hersch.

TABLE 2

Still births in Paris (1911-13) *by classes of arrondissements* (*Hersch*)

Classes of Arrondissements	Absolute figures		Still births per 100 living births
	Still births	Living births	
I	1,004	12,313	8.2
II	1,390	19,998	7.0
III	7,279	82,821	8.8
IV	3,024	30,853	9.8
Paris	12,679	145,985	8.7

This, indeed, he himself finds to be the fact when he considers the extremely sensitive index of hereditary biological constitution furnished by the still-birth rate. Table 2 gives the data. We see at once that there is no such striking increase in the total mortality as we pass from the richest class of districts, as was shown in the death rate from all causes. Instead there is practically no change, certainly none of significance, as we pass from one class of districts to another. The rate is 8.2 per 100 living births in the richest class and 9.8 in the poorest.

4. EXPERIMENTS ON TEMPERATURE AND DURATION OF LIFE

Altogether it is plain that we need another kind of evidence than the simple unanalyzed parallelism which Hersch demonstrates between poverty and the general death rate if we are to get any deep understanding of the influence of environmental circumstances upon the duration of life or the general death rate. We shall do well to turn again to the experimental method. About a dozen years ago Loeb,

> starting from the idea that chemical conditions in the organisms are one of the main variables in this case, raised the question whether there was a definite coefficient for the duration of life and whether this temperature coefficient was of the order of magnitude of that of a chemical reaction. The first experiments were made on the unfertilized and fertilized eggs of the sea urchin and could only be carried out at the upper temperature limits of the organism, since at ordinary temperatures this organism lives for years. In the upper temperature region the temperature coefficient for the duration of life was very high, probably on account of the fact that at this upper zone of temperature death is determined by a change of the nature of a coagulation or some other destructive process. Moore, at the suggestion of Loeb, investigated the temperature coefficient for the duration of life for the hydranth of a tubularian at the upper temperature limit and found that it was of the same order of magnitude as that previously found for the sea urchin egg. In order to prove that there is a temperature coefficient for the duration of life throughout the whole scale of temperatures at which an organism can live experiments were required on a form whose duration of life was short enough to measure the duration of life even at the lowest temperature.

A suitable organism was found in *Drosophila*. This was grown under aseptic conditions, as already described. The general results are shown in Table 3.

TABLE 3

Effect of temperature on duration of life of Drosophila.
(After Loeb and Northrop)

Temperature	Duration (in days) of			
	Larval stage	Pupal stage	Life of imago	Total duration of life from egg to death
°C				
10	57	Pupae die	120.5	177.5 + x
15	17.8	13.7	92.4	123.9
20	7.77	6.33	40.2	54.3
25	5.82	4.23	28.5	38.5
27.5	(4.15)	3·20	....	....
30	4.12	3.43	13.6	21.15

From this table it is seen that at the lowest temperature the duration of life is longest, and the highest temperature shortest. Cold slows up the business of living for the fly. Heat hastens it. One gathers, from the account which Loeb and Northrop give of the work, that at low temperature the flies are sluggish and inactive in all three developmental stages and perhaps live a long time because they live slowly. At high temperatures, on the other hand, the fly is very active and lives its life through quickly at the "pace that kills." These results are exactly comparable to the effect of a regular increase of temperature upon a chemical reaction. Indeed, Loeb and Northrop consider that their results prove that

> With a supply of proper and adequate food the duration of the larval stage is an unequivocal function of the temperature at which the larvae are raised, and the temperature coefficient is of the order of magnitude of that of a chemical reaction, i. e., about 2 or more for a difference of 10° C. It increases at the lower and is less at the higher temperatures. The duration of the pupal stage of the fly is also an unequivocal function of the temperature and the temperature coefficient is for each temperature practically identical with that for the larval stage. The duration of life of the imago is, with proper food, also an unequivocal function of the temperature and the temperature coefficient for the duration of life is within the normal temperature limits approximately identical with that for the duration of life of the larva and pupa.

How are these results to be reconciled with the previous finding that heredity is a primary factor in the determination of duration of life of *Drosophila?* We have here, on first impression at least, an excellent example of what one always encounters in critical genetic investigations: the complementary relations of heredity and environment. In our experiments a general mixed population of *Drosophila* kept under *constant environment* was shown to be separable by selection into a number of very diverse strains in respect of duration of life. In Loeb and Northrop's experiments a general mixed population of *Drosophila*, but of presumably *constant genetic constitution*, at least approximately such, throughout the experiment, was shown to exhibit changes of duration of life with changing environments. It is the old familiar deadlock. Heredity constant plus changing environment equals diversity. Environment constant plus varying hereditary constitution also equals diversity.

Can we penetrate no farther than this into the matter? I think in the present case we can. In Loeb and Northrop's experiments, temperature and duration of life were not the only two things that varied. The different temperature groups also differed from each other—*because* of the temperature differences to be sure but not less really—in respect of general metabolic *activity*, expressed in muscular movement and every other way. In the genetic experiments metabolic activity was substantially equal in all the hereditarily different lines. The idea suggests itself, both on *a priori* grounds and also upon the basis of certain experimental data presently to be in part reviewed, that possibly duration of life may be an implicit function of only the two variables

a. Genetic constitution
b. Rate of metabolic activity.

The functional relations of metabolic activity with temperature, food, light and other environmental factors are all well known. For present purposes we do not need to go into the question of their exact form. The essential point is that all these environmental factors stand in definite functional relations to rate of metabolic activity, and do not so stand in relation to genetic constitution. Genetic constitution is not a function of the environment, but is for any individual a constant, and only varies between individuals.

This may be thought merely to be an involved way of saying what one knows *a priori;* namely, that duration of life, in general and in particular, depends only upon heredity and environment. So in one sense it is. But the essential point I would make here is that the *manner in which the environmental forces (of sub-lethal intensity, of course) chiefly act in determining duration of life appears to be by changing the rate of metabolism of the individual.* Furthermore one would suggest, on this view, that what heredity does in relation to duration of life is chiefly *to determine, within fairly narrow limits, the total energy output which the individual can exhibit in its life time.* This limitation is directly brought about presumably through two general factors; viz, (a) the kind or quality of material of which this particular vital machine is built, and (b) the manner in which the parts are put together or assembled. Both of these factors are, of course, expressions of the extent and character of the processes of organic evolution which have given rise to this particular species about which we may be talking in a particular instance.

There is some direct experimental evidence, small in amount to be sure, but exact and pertinent, to the effect that the duration of life of an animal stands in inverse relation to the total amount of its metabolic activity, or put in other words, to the work, in the sense of theoretical mechanics, that it *as a machine* does during its life. Slonaker kept 4 albino rats in cages like the old fashioned revolving squirrel cages, with a properly calibrated odometer attached to the axle, so that the total amount of running which they did in their whole lives could be recorded. The results were those shown in Table 4.

TABLE 4

Relation of longevity to muscular activity in rats (Slonaker)

Total number of miles run during life

Age in months at death	Rat No. 1 Miles	No. 4 Miles	No. 2 Miles	No. 3 Miles
25	1265			
26		1391		
32			2098	
34				5447

It will be perceived that the amount of exercise taken by these rats was astonishingly large. For a rat to run 5,447 miles in the course of its life is indeed a remarkable performance. Now these 4 rats attained an average age at death of 29.5 months. But three control rats confined in stationary cages so that they could only move about to a limited degree, but otherwise under conditions, including temperature, identical with those in the revolving cages, attained an average age at death of 40.3 months. All were stated to have died of "old age." From this experiment it appears clearly that the greater the total work done, or total energy output, the shorter the duration of life, and *vice versa*. Or, put in another way, if the total activity per unit of time is increased by some means other than increasing temperature, the same results appear as if the increased activity is caused by increased temperature. It appears, in short, to be the activity *per se*, and not the temperature *per se* that is of real significance. There is other evidence, for which space lacks here, pointing in the same direction.

If we may be permitted to make a suggestion regarding the interpretation of Loeb and Northrop's results in conjunction with our own on *Drosophila*, it would be to this effect. Any given genetically pure strain of *Drosophila* is made up of individual machines, constructed to turn out before breaking down a definite limited amount of energy in the form of work, mechanical, chemical, and other. This definitely limited total energy output is predetermined by the hereditary constitution of the individual which fixes the kind of physicochemical machine that that individual is. But the *rate* per unit of time of the energy output may be influenced between wide limits by environmental circumstances in general and temperature in particular, since increased temperature increases rate of metabolic chemical changes in about the same ratio, as demonstrated by a wealth of work on temperature coefficients, as it increases other chemical changes. But if the rate of energy output per unit of time is changed, the total time taken for the total output of a predetermined amount of energy as work must change in inverse proportion to the change of rate. So we should expect just precisely the results on duration of life that Loeb and Northrop got, and so far from these results being in contradiction to ours upon heredity they may be looked upon as a necessary consequence of them. Loeb and Northrop's final conclusion is: "The observations on the temperature coefficient for the duration of life suggest that this duration is determined by the production of a substance leading to old age and natural death or by the destruction of a substance or substances which normally prevent old age and natural death." The view which I have here suggested completely incorporates this view within itself, if we suppose that the total amount of hypothetical "substance or substances which normally prevent old age and natural death" was essentially determined by heredity.

5. Gonads and Duration of Life

There is another and quite different line of experimental work on the duration of life which may be touched upon briefly. The daily press has lately had a great deal to say about rejuvenation accomplished by means of various surgical procedures undertaken upon the primary sex organs, particularly in the male. This newspaper notoriety has especially centered about the work of Voronoff and Steinach. The only experiments which at the present time probably deserve serious consideration are those of Steinach. He has worked chiefly with white rats. His theory is that by causing through appropriate operative procedure an extensive regeneration, in a senile animal about to die, of certain glandular elements of the testis, senility and natural death will for a time be postponed because of the internal secretion poured into the blood by the regenerated "puberty glands" as he calls them. The operation which he finds to be most effective is to ligate firmly the efferent duct of the testis, through which the sperm normally pass, close up to the testis itself and before the coiled portion of the duct is reached. The result of this, according to Steinach's account, is to bring about in highly senile animals a great enlargement of all the sex organs, a return of sexual activity previously lost through old age, and a general loss of senile bodily characteristics and a resumption of the conditions of full adult vigor in those respects.

Space is lacking to go into the many details of Steinach's work, much of which is indeed chiefly of interest only to the technical biologist, and from a wholly different standpoint than the present one. I should, however, like to present one example from his experiments. As control a rat was taken in the last degree senile. He was 26 months old when the experiment began. He was obviously emaciated, had lost much of his hair, particularly on the back and hind quarters. He was weak, inactive and drowsy, as indicated by the fact that his eyes were closed, and were, one infers from Steinach, kept so much of the time.

A litter brother of this animal had the efferent ducts of the testes ligated. This animal, we are told, was at the time of the operation, in so much worse condition of senility than his brother above described that it was not thought worth while even to photograph him. His condition was considered hopeless. To the surprise of the operator, however, he came back, slowly but surely after the operation, and after three and a half months presented a perfect picture of lusty young rathood. He was in full vigor of every sort, including sexual. He outlived his brother by 8 months, and himself lived 10 months after the operation, at which time he was, according to Steinach, practically moribund. This represents a presumptive lengthening of his expected span of life by roughly a quarter to a third. *It is to be remembered, however, that Slonaker's rats to which nothing was done lived to an average age of 40 months.*

The presumption that Steinach's experiments have really brought about a statistically significant lengthening of life is large, and the basis of ascertained fact small. After a careful examination of Steinach's brilliant contribution, one is compelled to take the view that however interesting the results may be from the standpoint of functional rejuvenation in the sexual sphere, the case is not proven that any really significant lengthening of the life span has occurred. In order to prove such a lengthening we must first of all have abundant and accurate quantitative data as to the normal variation of normal rats in respect of duration of life, and then show, having regard to the probable errors involved, that the mean duration of life after the operation has been significantly lengthened. This Steinach does not do. His paper is singularly bare of statistical data. We may well await adequate quantitative evidence before attempting any general interpretation of his results.

6. THE PITUITARY GLAND AND DURATION OF LIFE

Robertson has been engaged for a number of years past on an extensive series of experiments regarding the effect of various agents upon the growth of white mice. The experiments have been conducted with great care and attention to the proper husbandry of the animals. In consequence the results have a high degree of trustworthiness. In the course of these studies he found that the anterior lobe of the pituitary body, a small gland at the base of the brain, normally secretes into the blood stream minute amounts of an active substance which has a marked effect upon the normal rate of growth. By chemical means Robertson was able to extract this active substance from the gland in a fairly pure state and gave to it the name *tethelin*. In later experiments the effect of tethelin given by the mouth with the food was tried in a variety of ways.

In a recent paper Robertson and Ray have studied the effect of this material upon the duration of life of the white mouse with the results shown in Table 5.

TABLE 5

Effect of tethelin on duration of life in days of white mice.
(*Robertson and Ray*)

	MALES				FEMALES				Both sexes together
Class of animals	Average duration of life	Dev. from normal	$\frac{Dev.}{P.\ E.}$	Chance dev. was accidental	Average duration of life	Dev. from normal	$\frac{Dev.}{P.\ E.}$	Chance dev. was accidental	Chance dev. was accidental
Normal.....	767	----	----	------	719	----	----	-----	------
Tethelin....	866	+ 99	3.00	1:22.25	800	+ 81	2.25	1:6.75	1:150.2

From this table it is apparent that the administration of tethelin with the food from birth to death prolonged life to a degree which in the case of the males may be regarded as probably significant statistically. In the case of the females where the ratio of the deviation to its probable error (Dev. / P. E.) falls to 2.25 the case is very doubtful. The procedure by which the chance of 1:150.2 that results in both sexes together were accidental, was obtained is of doubtful validity. Putting males and females together from the original table I find the following results.

TABLE 6

Duration of life of white mice, both sexes taken together
(*From data of Robertson and Ray*)

Age Group	No. of deaths of normals (Both Sexes)	No. of deaths of tethelin fed (Both Sexes)
200-299	3	..
300-399	2	..
400-499	2	1
500-599	9	3
600-699	7	9
700-799	15	..
800-899	10	10
900-999	10	6
1000-1099	6	9
1100-1199	..	1
	64	39

Tethelin fed: Mean age at death $= 839 \pm 20$
Normal fed: Mean " " " $= 743 \pm 17$
Difference $= 96 \pm 26$

$$\frac{\text{Difference}}{\text{P. E.}_{\text{Diff.}}} = 3.7$$

One concludes from these figures that tethelin can be regarded as having lengthened the span of life to a degree which is just significant statistically. One would expect from the variation of random sampling alone to get as divergent results as these about 1¼ times in every 100 trials with samples of 64 and 39, respectively.

In any event it is apparent that, making out the best case possible, the differences in average duration of life produced by administration of tethelin are of a wholly different and smaller order than those which have been shown in the earlier portion of the paper to exist between pure strains of *Drosophila* which are based upon hereditary differences.

Putting together all the results which have been reviewed in this and the preceding paper, it appears to be clearly and firmly established that inheritance is the factor of prime importance in determining the normal, natural duration of life. In comparison with this factor the influence of environmental forces (of sub-lethal immediate intensity of course) appears in general to be less marked.